Stressors, Stress, and Neuroendocrine Integration of the Adaptive Response

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INTRODUCTION

Despite marked advances in stress research, confusion as to what stress is continues in the 1990s. Thus, it may be of benefit to briefly mention the definitions of four key concepts related to stress: those of homeostasis, stressor, stress, and adaptive response.[1] Life exists by maintaining a complex dynamic equilibrium, or *homeostasis*, that is constantly challenged by intrinsic or extrinsic adverse forces or *stressors*. *Stress* is, thus, defined as a state of threatened homeostasis, which is reestablished by a complex repertoire of *physiologic and behavioral adaptive responses* of the organism. The adaptive responses may be inadequate for the reestablishment of homeostasis or excessive and prolonged; in either case a healthy steady state is not attained, and pathology may ensue. With these straightforward definitions, the frequently interchangable use of the terms stress, stressor, and adaptive response will hopefully be avoided.

This review focuses on the neuroendocrine infrastructure of the adaptive response to stress and on its concerted effects on behavior, the major endocrine axes, and the gastrointestinal and immune systems. It also discusses the altered regulation or dysregulation of the adaptive responses in various physiologic and pathophysiologic states. These may influence the growth and development of an individual and may define the vulnerability of this individual to endocrine/metabolic/cardiovascular, psychiatric, or immunological disease, with their negative short- or long-term behavioral or physical sequelae. To avoid extensive referencing, several review articles containing many of the original references are included.

STRESS SYNDROME—PHENOMENOLOGY

The stress response is subserved by the *stress system* located in both the central nervous system (CNS) and the periphery.[2] This system receives and integrates a great diversity of neurosensory (higher cortical, limbic, visual, auditory, olfactory, gustatory, somatosensory, nociceptive, visceral) and blood-borne signals (blood composi-

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tion signals, hormones, cytokines, other mediators) that arrive through distinct pathways. Activation of the stress system leads to a cluster of time-limited behavioral and physical changes that are remarkably consistent in their qualitative presentation and collectively called the *general adaptation or stress syndrome* (TABLE 1). These changes are normally adaptive and improve the chances of the individual for survival. Components of the stress syndrome are stimulated in a stressor-specific fashion; however, as the potency of the stressor increases, the specificity of the response decreases to eventually produce the relatively "nonspecific" stress syndrome.

Behavioral adaptation includes increased arousal, alertness and vigilance, improved cognition, and focused attention, as well as euphoria or dysphoria, depending on the stressor and the memory of the organism. It also includes enhanced analgesia and elevations in core temperature, along with concurrent inhibition of vegetative functions, such as appetite, feeding, and reproductive function. Concomitantly, physical adaptation changes take place to principally promote an adaptive redirection of energy. Thus, oxygen and nutrients are shunted to the CNS and the stressed body site(s), where they are needed the most. Increases in cardiovascular tone (heart rate, cardiac ejection fraction, arterial blood pressure), respiratory rate, and intermediate metabolism (gluconeogenesis, lipolysis) all work in concert to promote availability of vital substrates. Detoxification functions to rid the organism of unnecessary metabolic products from the stress-related changes in metabolism are activated, while digestive function and growth, reproduction, and immunity are inhibited.

The organism also activates restraining forces during stress, which prevent an overresponse from both central and peripheral components the stress system. These forces are essential for successful adaptation. If they fail to contain the various elements of the stress response, the "adaptive" changes may turn excessive, prolonged, and maladaptive and may, thus, contribute to development of pathology.

Often stress is of a magnitude and nature that allows a perception of control by the individual. As such, stress can be pleasant and rewarding. The seeking of novelty stress by an individual is related to the above phenomenon and is pivotal for emotional and intellectual growth and development. It is of note that activation of

TABLE 1. Behavioral and Physical Adaptation during Acute Stress[a]

Behavioral Adaptation	Physical Adaptation
Adaptive Redirection of Behavior	**Adaptive Redirection of Energy**
Increased arousal and alertness	Oxygen and nutrients directed to the CNS and stressed body site(s)
Increased cognition, vigilance, and focused attention	Altered cardiovascular tone, increased blood pressure and heart rate
Euphoria or dysphoria	Increased respiratory rate
Suppression of appetite and feeding behavior	Increased gluconeogenesis and lipolysis
Suppression of reproductive behavior	Detoxification from endogenous or exogenous toxic products
Containment of the stress response	Inhibition of growth and reproductive systems
	Inhibition of digestion-stimulation of colonic motility
	Containment of the inflammatoryr/immmune response
	Containment of the stress response

[a]Adapted from Chrousos and Gold.[2]

the stress system occurs during both feeding and sexual activity, *sine qua non* functions for survival of self and species.

STRESS SYNDROME—PHYSIOLOGY "THE STRESS SYSTEM"

The central components of the stress system are located in the hypothalamus and the brainstem and include the parvocellular corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) neurons of the paraventricular nuclei (PVN) of the hypothalamus and the CRH neurons of the paragigantocellular and parabranchial nuclei of the medulla, as well as the locus ceruleus (LC) and other mostly noradrenergic (NE) cell groups of the medulla and pons (LC/NE-sympathetic system), referred to henceforth as the LC/NE system.[2] The peripheral limbs of the stress system are the hypothalamic–pituitary–adrenal (HPA) axis, together with the efferent sympathetic/adrenomedullary system, and components of the parasympathetic system.

CRH/AVP/Catecholaminergic Neurons

CRH, a 41 amino acid peptide, is the principal hypothalamic regulator of the pituitary–adrenal axis. The availability of synthetic CRH and peptidic CRH antagonists have allowed major advances in the investigation of stress.[2] Thus, CRH and CRH receptors were found in many extrahypothalamic sites of the brain, including parts of the limbic system, the basal forebrain, and the LC/NE system in the brainstem and spinal cord. In addition, intracerebroventricular administration of CRH was shown to set into motion a coordinated array of behavioral and peripheral responses, which included characteristic stress behaviors and activation of the pituitary–adrenal axis and the sympathetic nervous system. CRH, therefore, was found to have a broader role in coordinating the stress response than had been suspected previously. In fact, this neuropeptide fully reproduced the phenomenology of the stress response summarized in TABLE 1.

The central neurochemical circuitry responsible for activation of the stress system has been extensively studied and is summarized in FIGURE 1.[2,3] There are apparently multiple sites of interaction among the various components of the stress system. Reciprocal reverberatory neural connections exist between the PVN CRH and brainstem noradrenergic neurons of the central stress system, with CRH and norepinephrine stimulating each other, the latter primarily through α_1-noradrenergic receptors. Autoregulatory ultrashort negative-feedback loops are also present in both the PVN CRH and brainstem nonadrenergic neurons, with collateral fibers inhibiting CRH and catecholamine secretion, respectively, via presynaptic CRH and α_2-noradrenergic receptors. Both the CRH and catecholaminergic neurons also receive stimulatory innervation from the serotonergic and cholinergic systems and inhibitory input from the γ-aminobutyric acid (GABA)/benzodiazepine (BZD) and the opioid peptide neuronal systems of the brain, as well as by the end product of the HPA axis, glucocorticoids.

The secretion of CRH, a major anorexiogenic peptide, is stimulated by neuropeptide Y (NPY), the most potent orexiogenic factor known, which simultaneously inhibits the LC/NE-sympathetic system.[3] This may be of particular relevance to changes in stress system activity in states of dysregulation of food

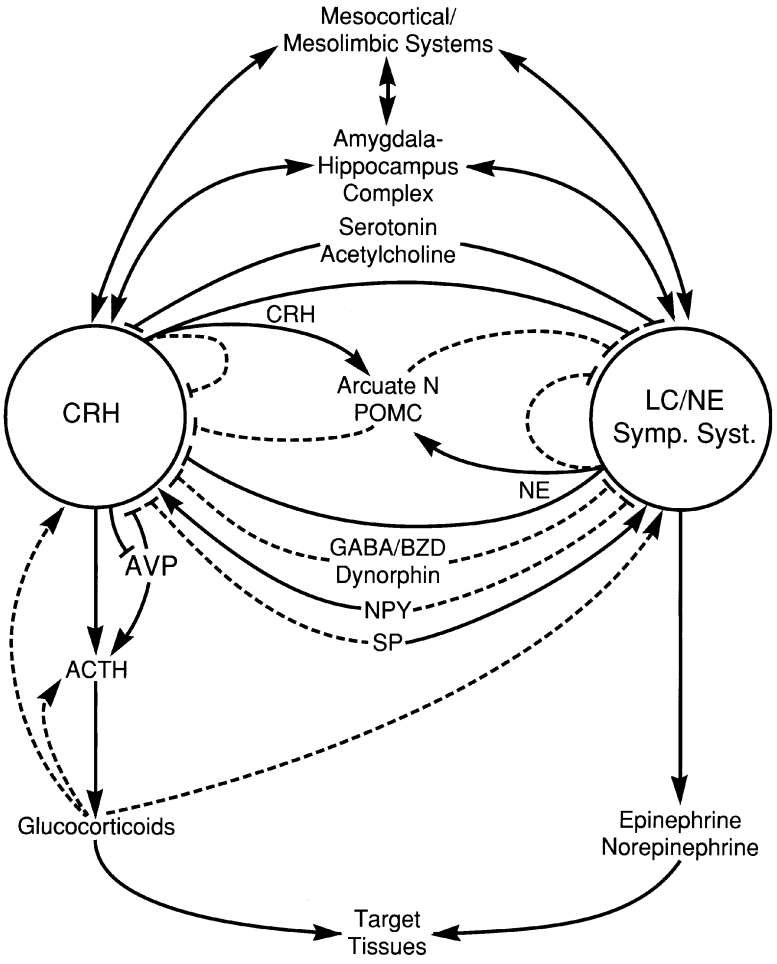

FIGURE 1. A simplified representation of the central and peripheral components of the stress system, their functional interrelations, and their relations to other central systems involved in the stress response. CRH, corticotropin-releasing hormone; LC/NE Symp. Syst., locus ceruleus/norepinephrine-sympathetic system; POMC, proopiomelanocortin; AVP, arginine vasopressin; GABA, γ-aminobutyric acid; BZD, benzodiazepine; ACTH, corticotropin; NPY, neuropeptide Y; SP, substance P. Activation is represented by *solid lines,* and inhibition by *dashed lines.* (Adapted from Chrousos and Gold.)

intake, including malnutrition, anorexia nervosa, and obesity. Interestingly, glucocorticoids stimulate hypothalamic NPY gene expression while they inhibit both the PVN CRH and LC/NE-sympathetic systems. The recently discovered leptin, an adipose tissue–derived hormone, exerts some of its effects on ingestive behavior and energy consumption via inhibition of NPY; the overall effect of leptin on CRH is to inhibit its secretion.[4]

Substance P (SP) has actions reciprocal to those of NPY, since it inhibits the PVN CRH neuron, while it activates the LC/NE system.[3] Presumably, substance P is elevated centrally, when there is peripheral activation of somatic afferent fibers and may, thus, have relevance to changes in the stress system activity in chronic inflammatory or painful states.

A subset of PVN parvocellular neurons synthesize and secrete both CRH and AVP, while another subset secretes AVP only.[2,3] The relative proportion of the subset that secretes both neuropeptides increases significantly during stress. The terminals of the parvocellular PVN CRH and AVP neurons project to different sites, including the noradrenergic neurons of the brainstem and the hypophysial portal system in the median eminence. PVN CRH and AVP neurons also send projections to and activate POMC-containing neurons in the arcuate nucleus of the hypothalamus, which in turn reciprocally project to the PVN CRH and AVP neurons, innervate LC/NE neurons of the central stress system in the brainstem, and terminate on pain control neurons of the hind brain and spinal cord.

The Hypothalamic–Pituitary–Adrenal Axis

CRH, released into the hypophyseal portal system, is the principal regulator of anterior pituitary corticotroph ACTH secretion.[2,3] It is permissive for secretion of ACTH, while AVP, though a potent synergistic factor of CRH, has very little ACTH secretagogue activity by itself. Further, it appears that there is a reciprocal positive interaction between CRH and AVP at the level of the hypothalamus with each neuropeptide stimulating the secretion of the other.

In nonstressful situations, both CRH and AVP are secreted in the portal system in a circadian and highly concordant pulsatile fashion.[5] The amplitude of the CRH and AVP pulses increase in the early morning hours, resulting eventually in increases of both the amplitude and apparent frequency of ACTH and cortisol secretory bursts in the general circulation. The circadian release of CRH, AVP, ACTH, and cortisol in their characteristic pulsatile manner appears to be controlled by one or more pacemakers, whose location is not yet known in humans. These diurnal variations are perturbed by changes in lighting, feeding schedules, and activity and are disrupted when a stressor is imposed.

During acute stress, the amplitude and synchronization of the PVN CRH and AVP pulsations in the hypophysial portal system increases.[5] Also, with strong physical stress, especially that associated with hypotension or a decrease of blood volume, recruitment of AVP of magnocellular neuron origin secreted into both the hypophyseal portal system via collateral neuraxons and into the systemic circulation takes place. Depending on the type of stress, other factors such as angiotensin II, as well as various cytokines and lipid mediators of inflammation are secreted and act on hypothalamic, pituitary, and/or adrenal components of the HPA axis mostly to potentiate its activity.

The adrenal cortex is the principal target organ of pituitary-derived circulating ACTH.[2,3] The latter is the key regulator of glucocorticoid and adrenal androgen secretion by the *zonae fasciculata* and *reticularis*, respectively, although it also participates in the control of aldosterone secretion by the *zona glomerulosa*. However, there is evidence that other hormones and/or cytokines, either originating from the adrenal medulla or coming from the systemic circulation, and/or neuronal information from the autonomic nerves of the adrenal cortex, may also participate in the regulation of cortisol secretion and the size of the adrenal cortexes.

Glucocorticoids are the final effectors of the HPA axis.[6,7] These hormones are pleiotropic and exert their effects through their ubiquitously distributed intracellular receptors. The nonactivated glucocorticoid receptor resides in the cytosol in the form of a heterooligomer with heat-shock proteins and immunophilins. Upon ligand binding, the glucocorticoid receptors dissociate from the rest of the heterooligomer and translocate into the nucleus, where they interact as homodimers with specific glucocorticoid-responsive elements (GREs) within the DNA to transactivate appropriate hormone-responsive genes. The activated receptors also inhibit, by protein–protein interactions, several transcription factors, such as c-*jun*/c-*fos* and NF-κB, which are positive regulators of the transcription of several genes involved in the activation of function and growth of nonimmune and immune cells. They also change the stability of mRNAs and, hence, the translation rates of several glucocorticoid-responsive proteins. Furthermore, glucocorticoids influence the secretion rates of specific proteins and alter the electrical potential of neuronal cells, through mechanisms that have not yet been elucidated.

The glucocorticoid sensitivity of target tissues is defined not only by the glucocorticoid receptor but also by other molecules that participate in the glucocorticoid signal transduction pathway: these include the heat-shock proteins, several transcription coregulator molecules, and other transcription factors.[7]

Glucocorticoids play a key regulatory role on the basal control of HPA axis activity and on the termination of the stress response by acting on extrahypothalamic regulatory centers, such as the hippocampus and frontal cortex, the hypothalamus, and the pituitary gland.[2,3] The inhibitory glucocorticoid feedback on the ACTH secretory response acts to limit the duration of the total tissue exposure to glucocorticoids, thus minimizing the catabolic, lipogenic, antireproductive, and immunosuppressive effects of these hormones. Interestingly, a dual receptor system exists for glucocorticoids in the central nervous system, including the glucocorticoid receptor type I, or mineralocorticoid receptor, which responds positively to low levels of glucocorticoids, and the classic glucocorticoid receptor (type II), which responds to both basal and stress levels. The latter participates in the negative feedback control of the HPA axis via activation of an afferent GABAergic pathway to the PVN.

The LC/NE Systemic/Adrenomedullary and Parasympathetic Systems

The autonomic nervous system responds rapidly to stressors and controls a wide range of functions.[2,3] Cardiovascular, respiratory, gastrointestinal, renal, endocrine and other systems are regulated by the sympathetic nervous system, the parasympathetic system, or both. Generally, the parasympathetic system can both assist sympathetic functions by withdrawing and antagonize them by increasing its activity.

Sympathetic innervation of peripheral organs is derived from the efferent preganglionic fibers, whose cell bodies lie in the intermediolateral column of the spinal cord. These nerves synapse in the bilateral chain of sympathetic ganglia with postganglionic sympathetic neurons that widely innervate the smooth muscle of the vasculature, heart, skeletal muscles, kidney, gut, fat, and many other organs. The preganglionic neurons are primarily cholinergic, whereas the postganglionic neurons are mostly noradrenergic. The sympathetic system through the adrenal medulla also has a humoral contribution because it provides all of the circulating epinephrine and some of the norepinephrine.

In addition to the "classic" neurotransmitters acetylcholine and norepinephrine, both sympathetic and parasympathetic subdivisions of the autonomic nervous system include several subpopulations of target-selective and neurochemically coded neurons that express a variety of neuropeptides and, in some cases, adenosine triphosphate (ATP), nitric oxide, or lipid mediators of inflammation. Thus, CRH, NPY, and somatostatin are found in postganglionic noradrenergic vasoconstrictive neurons. Transmission in sympathetic ganglia is also modulated by neuropeptides released from preganglionic fibers and short interneurons, as well as by primary afferent nerve collaterals.

STRESS SYSTEM INTERACTIONS WITH OTHER CNS COMPONENTS

In addition to setting the level of arousal and influencing the vital signs, the stress system also interacts with other major CNS elements, including the mesocorticolimbic dopaminergic system, the amygdala, the hippocampus, and the arcuate nucleus proopiomelanocortin (POMC) neuronal system.[2,3] All are activated during stress and, in turn, influence the activity of the stress system. In addition, the stress system interacts with the thermoregulatory and appetite-satiety centers of the CNS.

The Mesocorticolimbic System

Both the mesocortical and mesolimbic components of the dopaminergic system are innervated and activated by the LC/NE and PVN CRH systems and by glucocorticoids during stress. The mesocortical system, which includes dopaminergic neurons of the ventral tegmentum that send projections to the prefrontal cortex, is thought to be involved in anticipatory phenomena and cognitive functions and to exert a suppressive effect on the stress system. The mesolimbic system, which also consists of dopaminergic neurons also of the ventral tegmentum that innervate the nucleus accumbens, is believed to play a principal role in motivational/reinforcement/reward phenomena. Euphoria or dysphoria are presumably mediated by the mesocorticolimbic system, which is also the target of several substances of abuse, such as cocaine.

The Amygdala and Hippocampus

The amygdala is activated during stress primarily by ascending catecholaminergic neurons originating in the brainstem or by inner emotional stressors possibly generated in cortical association areas.[2,3] Activation of the amygdala is important for retrieval and emotional analysis of relevant information for any given stressor. In response to emotional stressors, the amygdala can directly stimulate both central components of the stress system, as well as influence the activity of the mesocorticolimbic dopaminergic system, possibly in a lateralized fashion. Interestingly, there are CRH peptidergic neurons in the central nucleus of the amygdala, which respond positively to glucocorticoids and whose activation leads to anxiety, fear, and stimulation of the stress system. The hippocampi exert an important, mostly inhibitory influence on the activity of the amygdala, as well as of the PVN CRH and LC/NE systems.

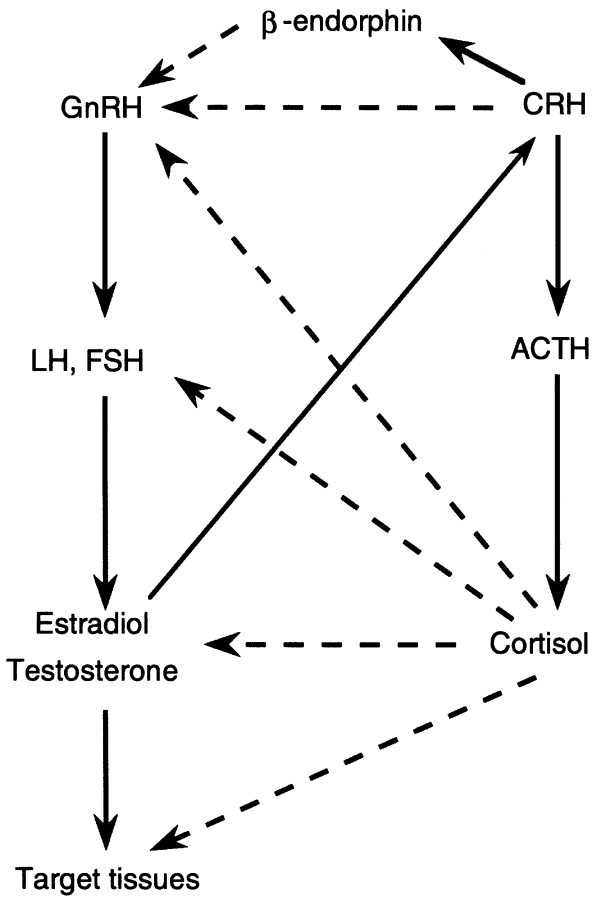

FIGURE 2A. Interactions between the HPA axis and the reproductive system. GnRH, gonadotropin-releasing hormone; LH, luteinzing hormone; FSH, follicle stimulating hormone. (Adapted from Chrousos and Gold.)

The POMC Neuronal System—Analgesia

PVN CRH/AVP-producing and LC/NE-noradrenergic neurons reciprocally innnervate and are innervated by opioid peptide (POMC-producing) neurons of the arcuate nucleus of the hypothalamus.[2,3,5] Activation of the stress system stimulates hypothalamic POMC peptide secretion, which reciprocally inhibits the activity of both central components of the stress system and in addition, through projections to the hindbrain and spinal cord, produces analgesia. POMC peptides

also stimulate the mesocorticolimbic system and hence may produce euphoria and dependence.

Temperature Regulation

Activation of the PVN CRH/AVP and LC/NE systems elevate core temperature. Both noradrenaline and CRH given intracerebroventricularly can cause core temperature increases, possibly through prostanoid-mediated actions on the septal and hypothalamic temperature-regulating centers. CRH has also been shown to mediate to some extent the pyrogenic effects of the inflammatory cytokines tumor necrosis factor-α (TNFα), interleukin-1 (IL-1), and interleukin-6 (IL-6), all of which can be stimulated by lipopolysaccharide, an exogenous pyrogen.

Appetite Regulation

The appetite/satiety centers in the hypothalamus are influenced by stress. Acutely, CRH causes anorexia, whereas NPY, which is orexiogenic, stimulates CRH secretion, probably to counteregulate its own actions. Interestingly, at the same time, NPY inhibits the LC/NE system and activates the parasympathetic system, actions that help with digestion and storage of nutrients. Leptin inhibits NPY and, hence, suppresses appetite and activates the LC/NE system, and, hence, increases peripheral energy expenditures.[4] Leptin also inhibits the PVN/CRH neuron system and other components of the HPA axis.

STRESS SYSTEM—INTERACTIONS WITH MAJOR ENDOCRINE AXES

The Reproductive Axis

The reproductive axis is inhibited at all levels by various components of the HPA axis[2] (FIG. 2**A**). Thus, either directly or via arcuate POMC neuron β-endorphin, CRH suppresses the gonadotropin-releasing hormone (GnRH) neurons of the arcuate and preoptic nuclei. Glucocorticoids, on the other hand, exert inhibitory effects at the levels of the GnRH neuron, the pituitary gonadotroph, influencing primarily the secretion of LH, and the gonads themselves, and render target tissues of sex steroids resistant to these hormones. During inflammatory stress, the inflammatory cytokines also suppress reproductive function at several levels. These effects are exerted both directly and by activating hypothalamic neural circuits that secrete CRH and POMC-derived peptides as well as by peripheral elevations of glucocorticoids.[5]

Suppression of gonadal function caused by chronic HPA activation has been demonstrated in highly trained runners of both sexes and ballet dancers as well as in individuals suffering from anorexia nervosa or starvation.[2,3,8] These subjects have increased evening plasma cortisol and ACTH levels, increased urinary free cortisol excretion, and blunted ACTH responses to exogenous CRH; males have low luteinizing hormone (LH) and testosterone levels, and females have hypogonadotrophic hypogonadism and amenorrhea. Characteristically, obligate athletes go through withdrawal symptoms and signs if, for any reason, they have to discontinue

their exercise routine. This syndrome is possibly the result of withdrawal from the daily exercise-induced secretion of POMC-derived peptides and mesocorticolimbic system dopamine.

The interaction between CRH and the reproductive axis appears to be bidirectional. The presence of estrogen responsive elements in the promoter area of the CRH gene and direct stimulatory estrogen effects on CRH gene expression were recently shown.[9] This finding implicates the CRH gene and, therefore, the HPA axis, as a potentially important target of gonadal steroids and a potential mediator of gender related differences in the stress response and HPA axis activity.[10,11]

Growth Axis

The growth axis is also inhibited at many levels during stress[2,3] (FIG. 2**B**). Prolonged activation of the HPA axis leads to suppression of growth hormone secretion and inhibition of somatomedin C and other growth factor effects on their target tissues by glucocorticoids, the latter possibly through inhibition of the c-*jun*/c-*fos* heterodimer by the ligand-bound glucocorticoid receptor.[6,7] However, acute elevations of growth hormone concentration in plasma may occur at the onset of the stress response or after acute administration of glucocorticoids, presumably through stimulation of the GH gene by glucocorticoids through GREs in its promoter region. In addition to the direct effects of glucocorticoids, which are pivotal in the suppression of growth observed in prolonged stress, increases in somatostatin secretion caused by CRH, with resultant inhibition of growth hormone secretion, have also been implicated as a potential mechanism of stress-related suppression of growth hormone secretion.

In several stress system–related mood disorders with a hyperactive HPA axis, such as chronic anxiety or melancholic depression, GH and/or insulin-like growth factor-1 (IGF-1) levels are significantly decreased.[12] Patients with panic disorder, compared to normal control subjects, have blunted GH responses to intravenously administered clonidine, and children with anxiety disorders might not attain their final height potential. In melancholic depression, not only is GH secretion decreased, but also the dexamethasone-induced GH increase is blunted.

Thyroid Axis

A corollary phenomenon to growth axis suppression is the stress-related inhibition of thyroid axis function[2] (FIG. 2**B**). Activation of the HPA axis is associated with decreased production of thyroid-stimulating hormone and inhibition of conversion of the relatively inactive thyroxine to the more biologically active triiodothyronine in peripheral tissues (the "euthyroid sick" syndrome). Both changes may be caused by the increased levels of glucocorticoids and apparently serve to conserve energy during stress. Inhibition of thyrotropin-releasing hormone and thyroid-stimulating hormone secretion by CRH-stimulated increases in somatostatin might also participate in the central component of thyroid axis suppression during stress. In the case of inflammatory stress, inhibition of TSH secretion, and blockade of peripheral 5′-deiodinase may be in part through direct action of inflammatory cytokines on the hypothalamic–pituitary unit and/or the peripheral tissues.

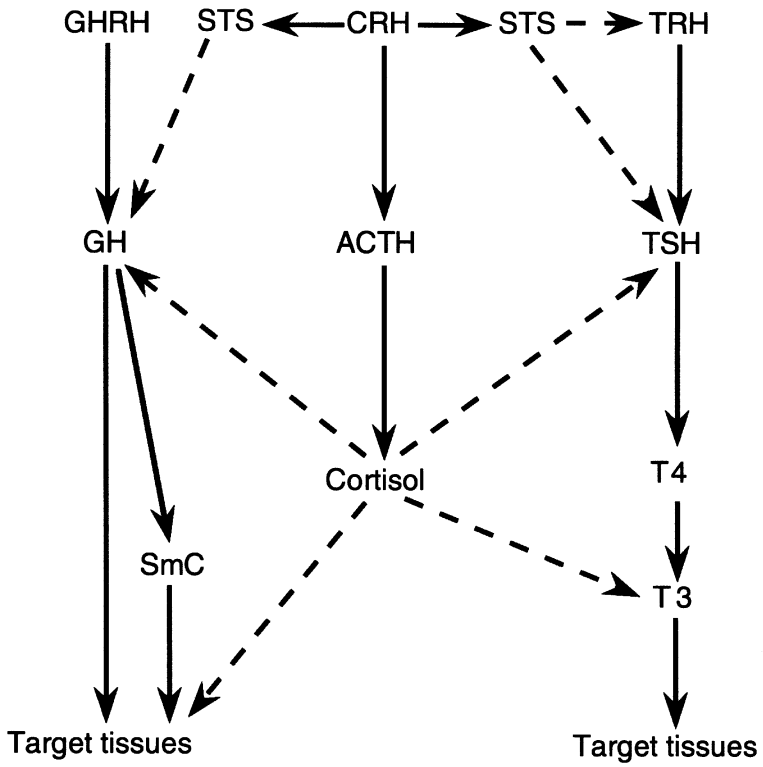

FIGURE 2B. Interactions of the HPA axis with the growth and thyroid axes. GHRH, growth hormone–releasing hormone; STS, somatostatin; TRH, thyrotropin releasing hormone; GH, growth hormone; TSH, thyroid-stimulating hormone; T_4, thyroxine; T_3, triiodothyronine; SmC, somatomedin C. (Adapted from Chrousos and Gold.)

Metabolic Axis

Glucocorticoids not only have profound inhibitory effects on GH and gonadal steroid production, but also antagonize the actions of these hormones on fat tissue catabolism (lipolysis), and muscle and bone anabolism[3] (FIG. 2**C**). Thus, chronic activation of the stress system would be expected to increase visceral adiposity, decrease lean body (bone and muscle) mass, and suppress osteoblastic activity. Interestingly, the phenotype of central obesity and decreased lean body mass is shared by patients with Cushing's syndrome and some patients with the combined diagnosis of melancholic depression or chronic anxiety disorder and the metabolic syndrome X (visceral obesity, insulin resistance, dyslipidemia, hypertension) or "pseudo-Cushing syndrome."[13]

Because increased gluconeogenesis is a characteristic feature of the stress response and glucocorticoids induce insulin resistance, activation of the HPA axis

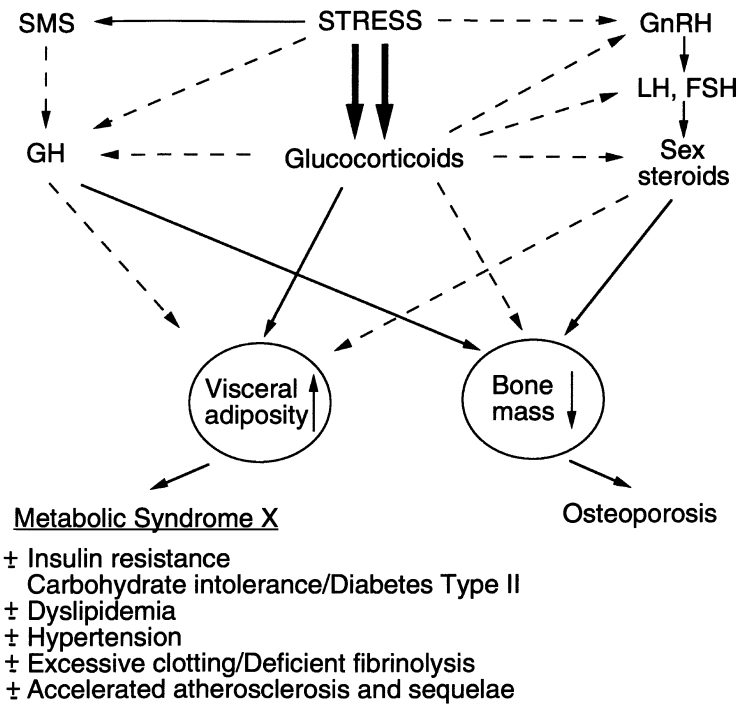

FIGURE 2C. Detrimental effects of chronic stress on adipose tissue metabolism and bone mass, SMS, somatostatin; GH, growth hormone. Stimulation is represented by *solid lines* and inhibition by *dashed lines.* (Adapted from Tsigos and Chrousos.)

may contribute to the poor control of diabetic patients during periods of emotional stress, or concurrently with inflammatory and other diseases. Indeed, mild, chronic activation of the HPA axis was recently demonstrated in diabetic patients under moderate or poor glycemic control.[14] Glucocorticoid-induced, progressively increasing visceral adiposity directly causes further insulin resistance and deterioration of glycemic control of patients with diabetes mellitus. Thus, chronic activation of the stress system in this disorder participates in a vicious cycle of increasing hyperglycemia, hypercholesterolemia, and insulin needs.

STRESS SYSTEM AND GASTROINTESTINAL FUNCTION

An increasing body of evidence suggests that CRH is involved in the central mechanisms by which stress influences gastrointestinal function (FIG. 3). Thus, PVN CRH induces both inhibition of gastric acid secretion and emptying and stimulation of colonic motor function, independently of the associated stimulation of the HPA axis.[3] This is via inhibition of the vagus nerve and ensuing selective

inhibition of gastric motility, and via stimulation—through the LC/NE system—of the sacral parasympathetic system, with ensuing selective stimulation of colonic motility. Thus, CRH may be implicated in mediating the gastric stasis that results from the stress of surgery. CRH may also be implicated in the stress-induced colonic hypermotility of patients with the irritable bowel syndrome. Colonic contraction and pain in these patients may further activate LC/NE system neurons, thus forming a chronic, stress-sustained vicious cycle.

STRESS SYSTEM–IMMUNE SYSTEM INTERACTIONS

Effects of the Immune/Inflammatory Reaction on the Stress System

The immune system exerts its surveillance–defense function constantly and mostly unconsciously for the individual. For several decades, it has been known that immune/inflammatory insults in the form of an infectious agent, an active autoimmune inflammatory process, or an accidental or operative trauma are associated with activation of the HPA axis. More, recently it also became apparent that cytokines and other humoral mediators of inflammation are potent activators of central stress-responsive neurotransmitter systems, constituting the afferent limb of a feedback loop from the immune/inflammatory system to the central nervous system[5] (FIG. 4). This way, the peripheral immunologic apparatus signals the brain to participate in maintaining "immunologic homeostasis."

The three "inflammatory cytokines" TNF-α, IL-1, and IL-6, produced in tandem at inflammatory sites and elsewhere in a cascade-like fashion, can cause stimulation of the HPA axis at all three levels *in vivo*, alone, or in synergy with each other.[5,15] This can be blocked significantly with CRH-neutralizing antibodies, prostanoid synthesis inhibitors, and glucocorticoids. In addition, all three cytokines directly stimulate hypothalamic CRH secretion *in vitro*, an action also suppressed by glucocorticoids and prostanoid synthesis inhibitors.

There is evidence to suggest that IL-6, the main endocrine cytokine, plays a primary role in the immune stimulation of the human HPA axis. Thus, in man, IL-6 is an extremely potent activator of the axis, importantly without the vascular leak-promoting and hypotensive side-effects of the other two inflammatory cytokines.[16,17] The elevations of ACTH and cortisol attained by IL-6 are well above those observed with maximal stimulatory doses of CRH, suggesting that parvocellular AVP and other ACTH secretagogues are also recruited by this cytokine. At high doses, IL-6 stimulates peripheral elevations of AVP, presumably as a result of a stimulatory effect on magnocellular AVP-secreting neurons.[18] This suggests that IL-6 may be involved in the genesis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), which is observed during the course of infectious/inflammatory disease or during trauma.

The route of access of the inflammatory cytokines to the central CRH and AVP-secreting neurons is not clear, given that the cellular bodies of both are protected by the blood–brain barrier.[15] It has been suggested that they may act on nerve terminals of these neurons at the median eminence through the fenestrated endothelia of this circumventricular organ. Other possibilities include stimulation of intermediate neurons located in the organum vasculosum of the lamina terminalis, another circumventricular organ. In addition, crossing the blood–brain barrier with the help of a specific transport system has not been excluded. Also, and

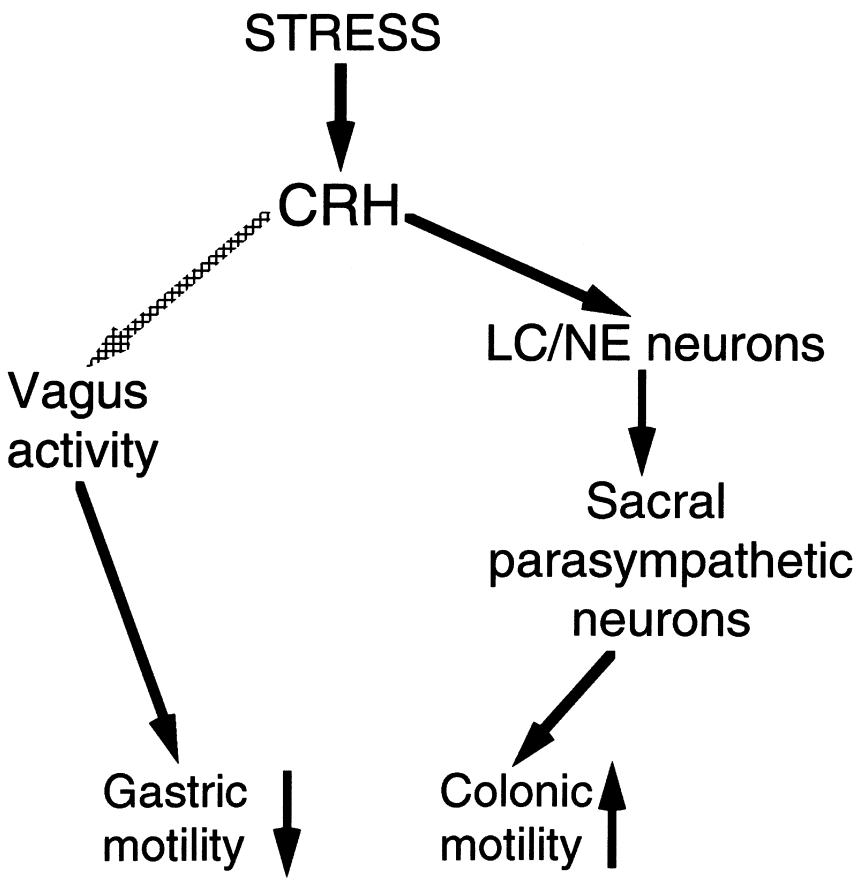

FIGURE 3. Effects of stress on gastrointestinal function. LC/NE, locus ceruleus/norepinephrine-sympathetic system. Stimulation is represented by *solid lines* and inhibition by *dashed lines.* (Adapted from Tsigos and Chrousos.)

quite likely, each of these cytokines might initiate a cascade of paracrine and autocrine events with sequential secretion of local mediators of inflammation by nonfenestrated endothelial cells, glial cells, and/or cytokinergic neurons, finally causing activation of CRH and AVP-secreting neurons.

Some of the activating effects of inflammation on the HPA axis may be exerted indirectly, by stimulation of the central noradrenergic pathways by the inflammatory cytokines and other humoral mediators of inflammation.[5] Also, activation of peripheral nociceptive, somatosensory, and visceral afferent fibers would lead to stimulation of both the LC/NE and PVN CRH neuronal systems via ascending spinal pathways. Interestingly, in chronic inflammatory states, where prolonged

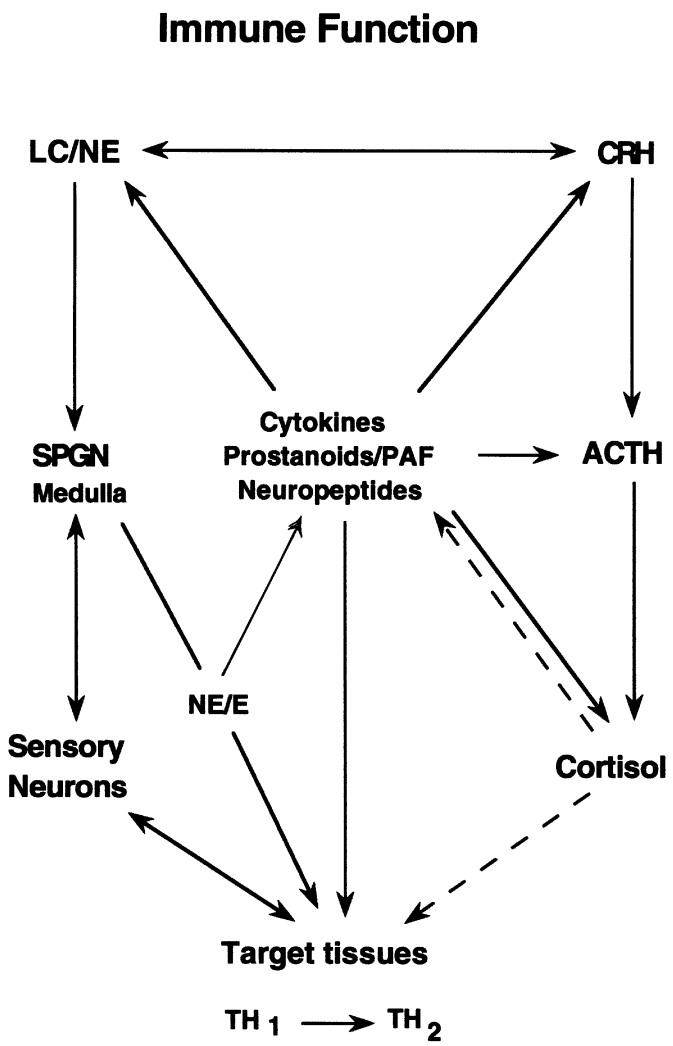

FIGURE 4. Interactions between the stress and immune systems. LC/NE, locus ceruleus/norepinephrine-sympathetic system; SPGN, sympathetic postganglionic neurons; CRH, corticotropin releasing hormone; ACTH, corticotropin; PAF, platelet activating factor. Stimulation is represented by *solid lines* and inhibition by *dashed lines.* (Adapted from Tsigos and Chrousos.)

central elevations of substance P may take place, an impairment of HPA axis responsiveness to stimuli or stress and a decrease in the CRH-to-AVP ratio are observed, probably because of the suppressive effect of substance P on the CRH neuron. Such changes have been observed in African trypanosomiasis, AIDS, and extensive burns in humans and in chronic animal models of inflammation.[19,20]

Other inflammatory mediators may also participate in the activation of the HPA axis, in addition to the three inflammatory cytokines. Thus, several eicosanoids, platelet activating factor (PAF), and epidermal growth factor show strong CRH-releasing properties.[21–23] It is not clear, however, which of the above effects are endocrine and which are autocrine or paracrine, with actions limited within the PVN. By no means are all signals from the immune system to the stress system stimulatory. Cytokines, such as TNFα, and growth factors, such as transforming growth factor β (TNFβ), have been shown to exert negative effects on the activity of the HPA axis.

Effects of the Stress System on the Immune/Inflammatory Reaction

Activation of the HPA axis has profound inhibitory effects on the inflammatory immune response, because virtually all the components of the immune response are inhibited by cortisol[5,24] (FIG. 4). At the cellular level, alterations of leukocyte traffic and function, decreases in production of cytokines and mediators of inflammation, and inhibition of the latter's effects on target tissues are among the main antiinflammatory and immunosuppressive effects of glucocorticoids. These effects are exerted at both the resting, basal state and during inflammatory stress, when the circulating concentrations of glucocorticoids are elevated. Thus, a circadian activity of several immune functions has been demonstrated in reversed-phase synchrony with that of plasma glucocorticoid levels.

A large infrastructure of anatomical, chemical, and molecular connections allows communication not only within but between the neuroendocrine and immune systems. The efferent sympathetic/adrenomedullary system apparently participates in a major fashion in the interactions of the HPA axis and immune/inflammatory stress by being reciprocally connected with the CRH system, by transmitting humoral and nervous signals to both primary and secondary lymphoid organs, and by reaching all sites of inflammation via the postganglionic sympathetic neurons. Thus, immune and immune accessory cells contain receptors for and respond to neurotransmitters, neuropeptides, and neurohormones secreted by postganglionic sympathetic neurons and/or the medulla. Of particular relevance is the mast cell, which is activated by products of these neurons, such as CRH. This may explain the induction by acute stress of allergic conditions, such as asthma and eczema, or of functional vascular diseases, such as migraine headaches.[25,26]

When activated during stress, the autonomic system also exerts systemic effects on immune organs humorally, by inducing secretion of IL-6 in the systemic circulation.[5] Despite its inherent inflammatory activity, IL-6, by causing glucocorticoid secretion and by directly suppressing the secretion of TNFα and IL-1, plays a major role in the overall, time-dependent control of inflammation.

The combination of cortisol and catecholamine elevations during stress can influence the T-helper (Th) phenotype of an individual by inhibiting interleukin-12 and stimulating interleukin-10 secretion by macrophages.[27] A transient shift from cellular to humoral immune response predominance would be adaptive in an acute situation but malaptive chronically, since it would make an individual vulnerable to certain infectious agents or tumors that are defended against primarily via cellular immune responses.

STRESS SYSTEM—PATHOPHYSIOLOGY

In theory, the dose–response curve between the responsiveness of the stress system and the potency of a stressor is represented by a sigmoidal curve, which would be expected to differ from individual to individual, with two major pathologic groups at the two extremes[2] (FIG. 5). Thus, one's dose–response curve might be shifted to the left of that of a normally reactive individual, while another's might be shifted to the right. The former denotes an excessive reaction, the latter a defective one. Similarly, the dose–response relation between one's sense of well-being or performance ability and the activity of the stress system are represented by an inverted U-shaped curve that covers the range of the activity of the latter. Shifts either to the left or to the right of this range, would, respectively, result in hypoarousal or hyperarousal (anxiety) and a suboptimal sense of well being and/or diminished performance.

Several of the multiple factors that determine the stress responses of individuals are inherited, as quantitative genetics of human complex behaviors indicate. It has been estimated that about half to two-thirds of reliable variance in measured personality traits is due to genetic influences. Thus, genetic polymorphisms and/or clinically significant alterations in the expression of genes involved in the regulation of the stress system (FIG. 1), such as, for example, those of CRH, AVP, and their receptors and regulators, are expected to account for the observed variability in the function of the stress system. A significant variance of the stress responses of individuals, however, is also environmental and this includes both early life and later life events with long-term or permanent effects.[2,28] The intrauterine period, infancy, childhood, and adolescence are periods of increased brain plasticity, thus, abnormal activation of the stress system during these critical

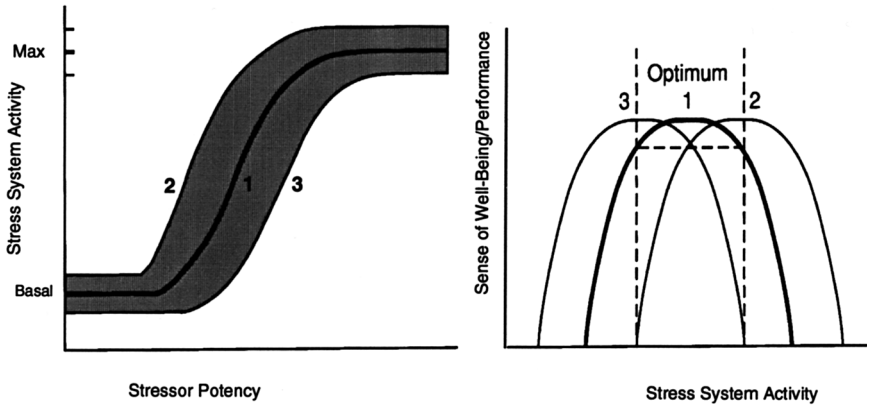

FIGURE 5. (Left) Dose–response curve between the potency of a stressor and the activity of the components of the stress system that are responsive to this stressor. If 1 is the normal curve, 2 shows hyperactivity, and 3 represents hypoactivity.

(Right) the inverse U-shaped relation between the activity of the stress system and the sense of well-being or quality of performance of an individual. Both excessive stress system activity, represented by curve 2, and diminished stress system activity, represented by curve 3, curtail the top of the inverse U-shaped curve, which represents the optimal activity. (Adapted from Chrousos and Gold.)

periods may have profound effects on its function throughout the life of an individual, causing predisposition to pathologic states.

Chronic Hyperactivation States

Generally, the stress response with the resultant activation of the HPA axis and LC/NE system is meant to be acute or at least of a limited duration. The time-limited nature of this process renders its accompanying antireproductive, antigrowth, catabolic, and immunosuppressive effects temporarily beneficial rather than adversive. Chronicity of stress system activation, on the other hand, may lead to a pathologic syndromal state.[2] Because CRH coordinates behavioral, neuroendocrine, autonomic, and immunologic adaptation during stressful situations, increased and prolonged production of CRH could explain the pathogenesis and all the manifestations of this syndrome, includings its psychiatric, neuroendocrine, cardiovascular, metabolic, and immune components. Each of these manifestations could be ameliorated or accentuated by the genetic and constitutional make-up of the individual.

The syndrome of adult melancholic depression represents a prototypic example of dysregulated activation of the generalized stress response, leading to dysphoric hyperarousal, chronic activation of the HPA axis and LC/NE system and relative immunosuppression[29,30] (TABLE 1). Indeed, cortisol excretion is increased and plasma ACTH response to exogenous CRH is decreased[31]; also, CSF levels of CRH are elevated in these patients.[32,33] These findings suggest that in depression, there is hypersecretion of CRH, which may participate in the initiation and/or perpetuation of a vicious cycle. Recently, depressed patients were found on autopsy to have markedly increased numbers of PVN CRH and AVP neurons.[34] Also, in two more recent imaging studies, depressed patients were found to have marked hippocampal atrophy[35] and a small and hypofunctioning section of the medial frontal lobe[36] (FIG. 6). Whether any of these changes are genetically determined, environmentally

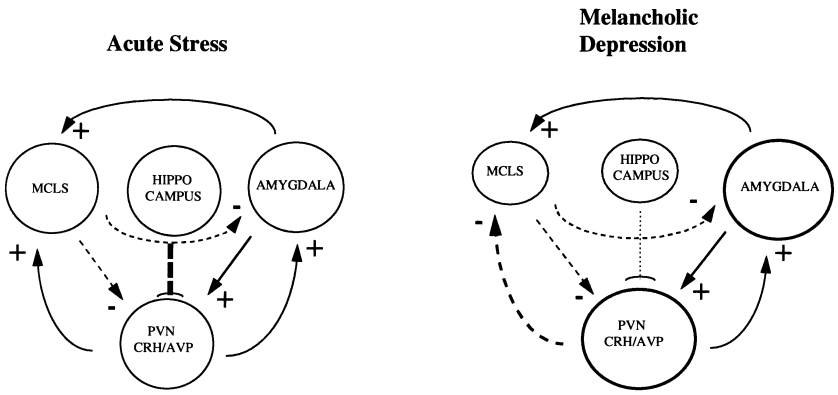

FIGURE 6. Central neurocircuitry in melancholic depression leading to a hyperactive stress system as it relates to the central neurocircuitry of the stress response. A hyperfunctioning amygdala, hypofunctioning hippocampus, and/or a hypofunctioning MCLS could predispose an individual to melancholic depression. MCLS=mesocorticolimbic system.

induced, or both is unclear at the present time. Yet, each and all of them could result in a hyperactive stress system and melancholic depression.

Because of their chronically or recurrently hyperactive stress system overtime, patients with melancholic depression may develop several severe somatic sequellae, such as osteoporosis, varying degrees and patterns of metabolic syndrome X, and Th_1 immunosuppression (FIG. 2**C**). Thus, a study of the mineral bone density of young women with recurrent depression revealed the presence of significant osteoporosis.[37] Plasma osteocalcin concentrations and urinary pyrinidinium cross-links were suppressed, revealing "low turnover" osteoporosis, similar to the one we observe in patients with Cushing's syndrome.

Over the years, we have seen a fair number of patients with melancholic depression, hypercortisolism, and obesity referred to our center for ruling out the diagnosis of Cushing's syndrome. We have devised a combined dexamethasone-ovine CRH test, which differentiates these patients with "pseudo-Cushing syndrome" from patients with *bona fide* Cushing's syndrome.[38] These patients have, in our opinion, depression-induced metabolic syndrome X, with some or all of its manifestations. In our hands, nondepressed obese subjects with or without manifestations of the metabolic syndrome X have normal cortisol production indices.[39]

In addition to osteoporosis and metabolic syndrome X, patients with melancholic depression develop varying degress of atherosclerosis and hence cardiovascular disease and Th_1 immunosuppression and hence certain infectious and neoplastic diseases. It is thus not surprising that these patients have a compromized life expectancy, which is courtailed by 15–20 years, after excluding suicides, the prevalence of which is increased in this group.

In addition to melancholic depression, a spectrum of other conditions may be associated with increased and prolonged activation of the HPA axis[2,3] (TABLE 2). These include anorexia nervosa and/or malnutrition, obsessive-compulsive disorder, panic anxiety, excessive exercising, chronic active alcoholism, alcohol and narcotic withdrawal, poorly controlled diabetes mellitus type I and II, childhood sexual abuse, and hyperthyroidism.

It is of interest that anorexia nervosa and malnutrition are characterized by increased levels of CSF NPY, which could provide an explanation for why the HPA axis in these subjects is activated, while the LC/NE system is characterized by marked hypoactivity.[3] Glucocorticoids, on the other hand, by stimulating NPY and by inhibiting the PVN CRH and the LC/NE systems, would produce the hyperphagia and obesity observed in Cushing's syndrome. A defect in the leptin system, such as that of the Zucker rat, is associated with hypersecretion of NPY and glucocorticoids and a hypofunctional LC/NE system leading to profound obesity.[40]

One area of recent interest relates to the association of chronic stress and gastrointestinal (GI) illness. In a study of patients with chronic GI pain, a high incidence of physically and sexually abused women was reported.[41] Sexually abused girls suffer from chronic activation of the HPA axis, as do patients with melancholic depression[42]. Thus, CRH hypersecretion could be the hidden link between the symptoms of chronic GI pain and other physical complaints and history of abuse.[43] Chronic activation of the HPA axis and/or the LC/NE system leading to chronic suppression of the arcuate nucleus POMC system may also explain the observed lower pain thresholds for visceral sensation in patients with functional GI disorders in whom glucocorticoid-induced suppression and tachyphylaxis of the opioid-peptide system may take place.

Psychosocial dwarfism is a term describing severe childhood or adolescent short stature and/or delayed puberty due to emotional deprivation or abuse.[12]

TABLE 2. States Associated with Altered Hypothalamic–Pituitary–Adrenal Axis Activity and Altered Regulation or Dysregulation of Behavioral and/or Peripheral Adaptation[a]

Increased HPA Axis	Decreased HPA Axis
Chronic stress	Adrenal insufficiency
Melancholic depression	Atypical/seasonal depression
Anorexia nervosa	Chronic fatigue syndrome
Malnutrition	Fibromyalgia
Obsessive–compulsive disorder	Hypothyroidism
Panic disorder	Nicotine withdrawal
Excessive exercise (obligate athleticism)	After stopping glucocorticoid therapy
Chronic active alcoholism	Postpartum period
Alcohol and narcotic withdrawal	After chronic stress
Diabetes mellitus	Rheumatoid arthritis
Childhood sexual abuse	Premenstrual tension syndrome
Psychosocial short stature	Climacteric depression
"Functional" gastrointestinal disease	
Hyperthyroidism	
Cushing syndrome	
Pregnancy (last trimester)	

[a]Adapted from Chrousos and Gold.[2]

Decreased GH secretion that is reversible after separation of the child from the responsible environment, is a characteristic finding in this condition, which is also associated with a variety of behavioral abnormalities, such as depression and pica and other bizarre eating behaviors. In addition to low GH secretion, these patients have a dysfunctional thyroid axis, resembling the "euthyroid sick" syndrome. Interestingly, we know very little about the HPA axis in children with this condition, however, we suspect that at least its central component is chronically activated, and this would explain all the other endocrine and growth abnormalities they have.

Pregnancy in the third trimester is another condition characterized by hypercortisolism of a degree similar to that observed in severe depression, anorexia nervosa, and mild Cushing syndrome, the only known physiologic state in humans in which CRH circulates in plasma at levels high enough to cause activation of the HPA axis.[44] Although circulating CRH, which is of placental origin, is bound with high affinity to CRH-binding protein, it appears that the circulating free fraction is sufficient to explain the observed escalating hypercortisolism when the concentration of CRH binding protein starts to gradually decrease in plasma after the 35th week of pregnancy.

The recent development of nonpeptidic CRH receptor antagonists that cross the blood–brain barrier and have very promising actions in preclinical studies in rats and monkeys, offer us a new major opportunity to intervene in states in which excessive CRH secretion appears to play a key pathophysiologic role[45] (FIG. 7). Melancholic depression, anorexia nervosa, obsessive compulsive disorder and withdrawal from certain narcotic agents are only a few of the target diseases that will be evaluated in the near future.

Chronic Hypoactivation States

Hypoactivation of the stress system, rather than sustained activation, in which chronically reduced secretion of CRH may result in pathological hypoarousal,

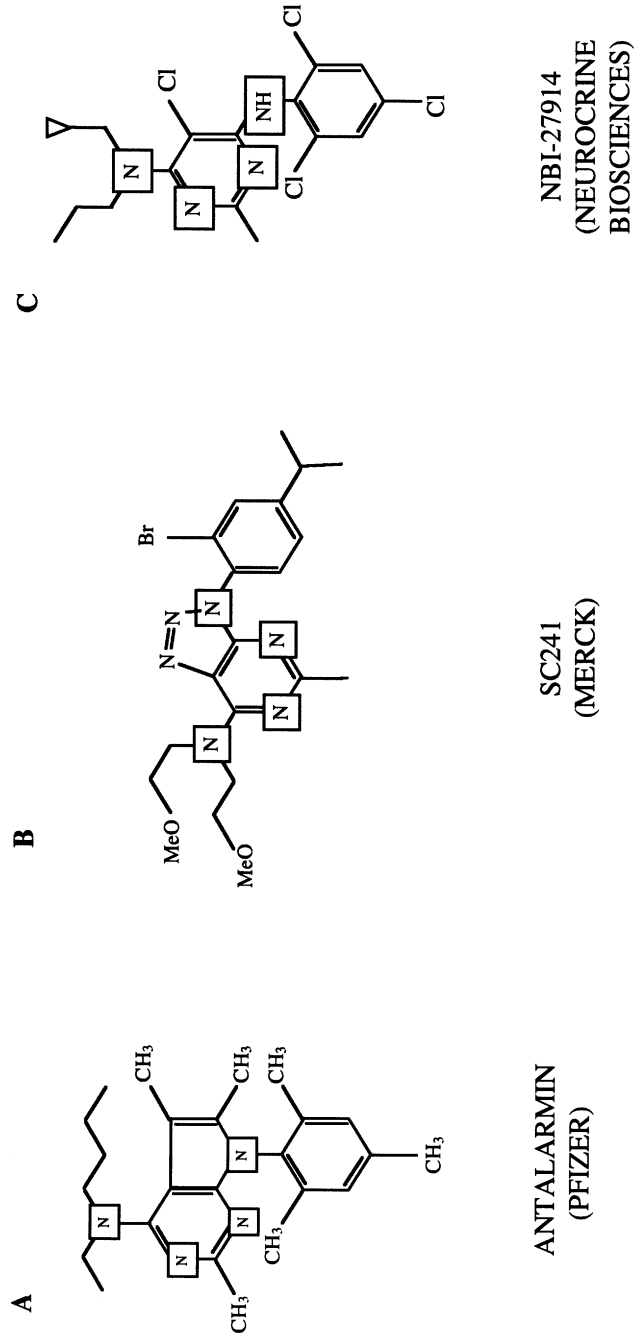

FIGURE 7. The three classes of recently described nonpeptidic CRH receptor 1 antagonists.

characterizes another group of states[2] (TABLE 2). Patients with atypical seasonal depression and chronic fatigue syndrome fall into this category.[46, 47] In the depressive (winter) state of the former and in the period of fatigue in the latter, there is decreased activity of the HPA axis. Similarly, patients with fibromyalgia have decreased urinary free cortisol excretion and frequently complain of fatigue.[48] Hypothyroid patients also have clear evidence of CRH hyposecretion. Interestingly, one of the major manifestations of hypothyroidism is depression of the "atypical" type.

Withdrawal from smoking has also been associated with decreased cortisol and catecholamine secretion.[2] Decreased CRH secretion in the early period of nicotine abstinence could explain the hyperphagia, hypometabolism, and weight gain frequently observed in these patients. It is interesting that in Cushing syndrome, the clinical picture of atypical depression, hyperphagia, and weight gain, as well as fatigue and anergia, is consistent with the suppression of the CRH neuron by the associated hypercortisolism.[49] The period after the cure of hypercortisolism, the post-partum period, and periods following cessation of chronic stress are also associated with atypical depression, suppressed PVN CRH secretion and decreased HPA axis activity.[50,51]

Theoretically, an excessive HPA axis response to inflammatory stimuli would mimic the stress or hypercortisolemic state and would lead to increased susceptibility of the individual to a host of infectious agents or tumors as a result of T-helper-1 suppression, but enhanced resistance to autoimmune/inflammatory diseases; in contrast, a defective HPA axis response to such stimuli would reproduce the glucocorticoid-deficient state and would lead to relative resistance to infections and neoplastic diseases, but increased susceptibility to T-helper-1–mediated autoimmune/inflammatory diseases, such as Hashimoto thyroiditis or rheumatoid arthritis.[5]

Indeed, such properties were unraveled in an interesting pair of near-histocompatible, highly inbred rat strains, the Fischer and Lewis rats, respectively, for their resistance or susceptibility to inflammatory disease.[5] There is now an increasing body of evidence that patients with rheumatoid arthritis have increased incidence of atypical depression, as well as a mild form of central hypocortisolism, as they have paradoxically normal 24-hour cortisol excretion and blunted adrenal responses to surgical stress.[52,53] Thus, dysfunction of the HPA axis may actually play a role in the development and/or perpetuation of autoimmune disease, rather than being an epiphenomenon. The same rationale may explain the high incidence of autoimmune disease in the period after cure of hypercortisolism and the postpartum period, as well as in glucocorticoid unreplaced or underreplaced adrenal insufficiency.[51]

REFERENCES

1. CHROUSOS, G. P., D. L. LORIAUX & P. W. GOLD. 1988. The concept of stress and its historical development. *In* Mechanisms of Physical and Emotional Stress. Plenum. New York. Adv. Exp. Med. Biol. **245**: 3–7.
2. CHROUSOS, G. P. & P. W. GOLD. 1992. The concepts of stress and stress system disorders: Overview of physical and behavioral homeostasis. JAMA **267**: 1244–1252.
3. TSIGOS, C. & G. P. CHROUSOS. 1995. Stress, endocrine manifestations and diseases. Chapter 3. *In* Handbook of Stress Medicine. C. L. Cooper, Ed.: 61–65. CRC Press. Boca Raton, FL.

4. LICINIO, J., C. MANTZOROS, A. B. NEGRÃO, G. CIZZA, M. L. WONG, P. B. BONGIORNO, G. P. CHROUSOS, B. KARP, C. ELLEN, J. S. FLIER & P. W. GOLD. 1997. Human leptin levels are pulsatile and inversely related to pituitary–adrenal function. Nat. Med. **3**: 575–579.
5. CHROUSOS, G. P. 1995. The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. N. Engl. J. Med. **332**: 1351–1362.
6. CHROUSOS, G. P., S. DETERA-WADLEIGH & M. KARL. 1993. Syndromes of glucocorticoid resistance. Ann. Int. Med. **119**: 1113–1124.
7. BAMBERGER, C. M., H. M. SCHULTE & G. P. CHROUSOS. 1996. Molecular determinants of glucocorticoid receptor function and tissue sensitivity. Endocrinol. Rev. **17**: 221–244.
8. LUGER, A., P. DEUSTER, S. B. KYLE, W. T., GALLUCCI, L. C. MONTGOMERY, P. W. GOLD, D. L. LORIAUX & G. P. CHROUSOS. 1987. Acute hypothalamic–pituitary–adrenal responses to the stress and treadmill exercise physiologic adapatations to physical training. N. Engl. J. Med. **316**: 1309–1315.
9. VAMVAKOPOULOS, N. C. & G. P. CHROUSOS. 1993. Evidence of direct estrogen regulation of human corticotropin releasing hormone gene expression: Potential implications for the sexual dimorphism of the stress response and immune/inflammatory reaction. J. Clin. Invest. **92**: 1896–1902.
10. GALLUCCI, W. T., A. BAUM, L. LAUE, D. S. RABIN, G. P. CHROUSOS, P. W. GOLD & M. A. KLING. 1993. Sex differences in sensitivity of the hypothalamic–pituitary–adrenal axis. Health Psychol. 12: 420–425.
11. VAMVAKOPOULOS, N. C. & G. P. CHROUSOS. 1994. Hormonal regulation of human corticotropin releasing hormone gene expression: Implications for the stress response and immune/inflammatory reaction. Endocrinol. Rev. **15**: 409–420.
12. CHROUSOS, G. P. 1997. The neuroendocrinology of stress: Its relation to the hormonal milieu, growth, and development. Growth Genet. & Horm. **13**: 1–8.
13. FRIEDMAN, T. C., G. MASTORAKOS, T. D. NEWMAN, N. M. MULLEN, E. G. HORTON, R. COSTELLO, N. M. PAPADOPOULOS & G. P. CHROUSOS. 1996. Carbohydrate and lipid metabolism in endogenous hypercortisolism: Shared features with metabolic syndrome X and noninsulin-dependent diabetes mellitus. Endocr. J. **43**: 645–656.
14. ROY, M. S., A. ROY, W. T. GALLUCCI, B. COLLIER, K. YOUNG, T. C. KAMILARIS & G. P. CHROUSOS. 1993. The ovine corticotropin releasing hormone test in type I diabetic patients and controls: Suggestion of mild chronic hypercortisolism. Metabolism **42**: 696–700.
15. PAPANICOLAOU, D. A., R. L. WILDER, S. C. MANOLAGAS & CHROUSOS G. P. 1998. The pathophysiologic roles of interleukin-6 in humans. Ann. Intern. Med. **128**: 127–137.
16. MASTORAKOS, G., G. P. CHROUSOS & J. WEBER. 1993. Recombinant interleukin-6 activates the hypothalamic–pituitary–adrenal axis in humans. J. Clin. Endocrinol. Metab. **27**: 1690–1694.
17. TSIGOS, C., D. A. PAPANICOLAOU, R. DEFENSOR, C. S. MITSIADES, I. KYROU & G. P. CHROUSOS. 1997. Dose effects of recombinant human interleukin-6 on pituitary hormone secretion and energy expenditure. Neuroendocrinology **66**: 54–62.
18. MASTORAKOS, G., J. S. WEBER, M. A. MAGIAKOU, H. GUNN & G. P. CHROUSOS. 1994. Hypothalamic–pituitary–adrenal axis activation and stimulation of systemic vasopressin secretion by recombinant interleukin-6 in humans: Potential implications for the syndrome of inappropriate vasopressin secretion. J. Clin. Endocrinol. Metab. **79**: 1191–1197.
19. REINCKE, M., B. ALLOLIO, W. ARLT, C. HEPPNER, F. PETCKE, D. MBULAMBERI, L. SIEKMAN, D. VOLLMER, W. WINKLEMAN & G. P. CHROUSOS. 1994. Impairment of adrenocortical function associated with increased plasma tumor necrosis factor-α and interleukin-6 concentrations in African trypanosomiasis. NeuroImmunoModulation **1**: 14–22.
20. MICHELSON, D., L. STONE, E. GALLIVEN, M. A. MAGIAKOU, G. P. CHROUSOS, E. M. STERNBERG & P. W. GOLD. 1994. Multiple scelrosis is associated with alterations in hypothalamic–pituitary–adrenal function. J. Clin. Endocrinol. Metab. **79**: 848–853.
21. BERNARDINI, R., A. CALOGERO, G. MAUCERI & G. P. CHROUSOS. 1990. Rat hypothalamic corticotropin releasing hormone secretion *in vitro* is stimulated by interleukin-1 in an eicosanoid-dependent manner. Life Sci. **47**: 1601–1607.

22. BERNARDINI, R., A. CHIARENZA, A. E. CALOGERO, P. W. GOLD & G. P. Chrousos. 1989. Arachidonic acid metabolites modulate rat hypothalamic corticotropin releasing hormone secretion *in vitro*. Neuroendocrinology **50**: 708–715.
23. LUGER, A., A. CALOGERO, K. KALOGERAS, W. GALLUCCI, P. W. GOLD, D. L. LORIAUX & G. P. CHROUSOS. 1987. Interaction of epidermal growth factor with the hypothalamic–pituitary–adrenal axis: Potential physiologic relevance. J. Clin. Endocrinol. Metab. **66**: 334–337.
24. BOUMPAS, D. T., G. P. CHROUSOS, R. L. WILDER, T. R. CUPPS & J. E. BALOW. 1993. Glucocorticoid therapy of immune-related diseases: Basic and clinical correlates. Ann. Inter. Med. **119**: 1198–1208.
25. WEBSTER, E. L., I. J. ELENKOV & G. P. CHROUSOS. 1997. The role of corticotropin-releasing hormone in neuroendocrine–immune interactions. Mol. Psychiatry **2**: 368–372.
26. THEOHARIDES, T. C., C. SPANOS, Z. PANG, L. ALFERES, K. LIGRIS, R. LETOURNEAU, J. J. ROZNIECKI, E. L. WEBSTER & G. P. CHROUSOS. 1995. Stress-induced intracranial mast cell degranulation: A corticotropin-releasing hormone-mediated effect. Endocrinology **136**: 5745–5750.
27. ELENKOV, I. J., D. A. PAPANICOLAOU, R. L. WILDER & G. P. CHROUSOS. 1996. Modulatory effects of glucocorticoid and catecholamines on human interleukin-12 and interleukin-10 production: Clinical implications. Proc. Assn. Am. Phys. **108**: 374–381.
28. CHROUSOS, G. P. 1997. The future of pediatric and adolescent endocrinology. Ann. N.Y. Acad. Sci. **816**: 4–8.
29. GOLD, P. W., F. GOODWIN & G. P. CHROUSOS. 1988. Clinical and biochemical manifestations of depression: Relationship to the neurobiology of stress (Part I). N. Engl. J. Med. **319**: 348–353.
30. GOLD, P. W., F. GOODWIN & G. P. CHROUSOS. 1988. Clinical and biochemical manifestations of depression: Relationship to the neurobiology of stress (Part II). N. Engl. J. Med. **319**: 413–420.
31. GOLD, P. W., D. L. LORIAUX, A. ROY, M. A. LINK, J. R. CALABRESE, C. H. KELLNER, L. K. NIEMAN, R. M. POST, D. PICKAR, W. GALLUCCI, P. AVGERINOS, S. PAUL, E. H. OLDFIELD, G. B. CUTLER, JR. & G. P. CHROUSOS. 1986. Responses to corticotropin releasing hormone in the hypercortisolism of depression and Cushing's disease: Pathophysiologic and diagnostic implications. N. Engl. J. Med. **314**: 1329–1335.
32. ROY, A., D. PICKAR, S. PAUL, A. DORAN & G. P. CHROUSOS. 1987. CSF corticotropin releasing hormone in depressed patients and normal control subjects. Am. J. Psychiatry **114**: 641–645.
33. KLING, M. A., A. DORAN, D. R. RUBINOW, A. ROY, R. M. POST, G. P. CHROUSOS & P. W. GOLD. 1991. CSF levels of CRH, ACTH and SRIF in Cushing's syndrome, major depression, and normal volunteers: Physiological and pathophysiological interrelationships. J. Clin. Endocrinol. Metab. **72**: 260–271.
34. RAADSHEER, F. C., W. J. HOODENDIJK, F. S. STAM, F. J. H. TILDERS & D. F. SWAAB. 1994. Increased numbers of corticotropin-releasing hormone expresing neurons in the hypothalamic paraventricular nucleus of depressed patients. Neuroendocrinology **60**: 436–444.
35. SHELINE, Y. I., P. W. WANG, M. H. GADO, J. G. CSERNANSKY & M. W. VANNIER. 1996. Hippocampal atrophy in recurrent major depression. Proc. Natl. Acad. Sci. USA **93**: 3908–3913.
36. DREVETS, W. C., J. L. PRICE, J. R. SIMPSON, JR., R. D. TODD, T. REICH, M. VANNIER & M. E. RAICHLE. 1997. Subgenual prefrontal cortex abnormalities in mood disorders. Nature **386:** 824–827.
37. MICHELSON, D., C. STRATAKIS, L. Y. HILL, J. REYNOLDS, E. GALLIVEN, G. P. CHROUSOS & P. W. GOLD. 1996. Bone mineral density is decreased in women with depression. N. Engl. J. Med. **335**: 1176–1181.
38. YANOVSKI, J. A., G. B. CUTLER, JR., G. P. CHROUSOS & L. K. NIEMAN. 1993. Corticotropin-releasing hormone stimulation following low-dose dexamethasone administration: A new test to distinguish Cushing's syndrome from Pseudo-Cushings states. JAMA **269**: 2232–2238.

39. YANOVSKI, J. A., S. Z .YANOVSKI, P. W. GOLD & G. P. CHROUSOS. 1997. Differences in corticotropin-releasing hormone-stimulated adrenocorticotropin and cortisol before and after weight loss. J. Clin. Endocrinol. Metab. **82**: 1874–1878.
40. PACAK, K., R. MCCARTY, M. PALKOVITZ, G. CIZZA, I. J. KOPIN, D. GOLDSTEIN & G. P. CHROUSOS. 1995. Decreased central and peripheral catecholaminergic activation in obese Zucker rats. Endocrinology **136**: 4360–4367.
41. SCARINCI, I. C., J. MCDONALD-HAILE, L. A. BRADLEY, J. E. RICHTER. 1994. Altered pain perception and psychosocial features among women with gastrointestinal disorders and history of abuse: A preliminary model. Am. J. Med. **97**: 108–118.
42. DEBELLIS, M., G. P. CHROUSOS, L. DORN, L. BURKE, K. HELMERS, M. A. KLING, P. K. TRICKETT & F. W. 1994. Putnam. Hypothalamic–pituitary–adrenal axis dysregulation in sexually abused girls. J. Clin. Endocrinol. Metab. **78**: 249–255.
43. MCCAULEY, J., D. E. KERN, K. KOLODNER, L. HILL, A. F. SCHROEDER, H. K. DECHANT, J. RYDEN, L. R. DEROGATIS & E. B. BASS. 1997. Clinical characteristics of women with a history of childhood abuse. JAMA **277**: 1362–1368.
44. MAGIAKOU, M. A., G. MASTORAKOS, D. RABIN, A. N. MARGIORIS, B. DUBBERT, A. E. CALOGERO, C. TSIGOS, P. J. MUNSON & G. P. CHROUSOS. 1996. The maternal hypothalamic–pituitary–adrenal axis in third trimester human pregnancy. Clin. Endocrinol. **44**: 419–428.
45. WEBSTER, E. L., D. B. LEWIS, D. J. TORPY, K. E. ZACHMAN, K. C. RICE & CHROUSOS GP. 1996. *In vivo* and *in vitro* characterization of antalarmin, a nonpeptide corticotropin-releasing hormone (CRH) receptor antagonist: Suppression of pituitary ACTH release and peripheral inflammation. Endocrinology **137**: 5747–5750.
46. VANDERPOOL, J., N. ROSENTHAL, G. P. CHROUSOS, T. WEHR, R. SKEWERER, S. KASPER & P. W. GOLD. 1991. Evidence for hypothalamic CRH deficiency in patients with seasonal affective disorder. J. Clin. Endocrinol Metab. **72**: 1382–1387.
47. DEMITRACK, M., J. DALE, S. STRAUS, L. LAUE, S. LISTWAK, M. KRUESI, G. P. CHROUSOS & P. W. GOLD. 1991. Evidence of impaired activation of the hypothalamic–pituitary–adrenal axis in patients with chronic fatigue syndrome. J. Clin. Endocrinol. Metab. **73**: 1224–1234.
48. CROFFORD, L. J., S. R. PILLEMER, K. T. KALOGERAS, J. M. CASH, D. MICHELSON, M. A. KLING, E. M. STERNBERG, P. W. GOLD, G. P. CHROUSOS & R. L. WILDER. 1994. Hypothalamic–pituitary–adrenal axis perturbation in patients with fibromyalgia. Arthritis and Rheumatism **37**: 1583–1592.
49. DORN, L. D., E. S. BURGESS, B. DUBBERT, M. KLING, P. W. GOLD & G. P. CHROUSOS. 1995. Psychopathology in patients with endogenous Cushing's syndrome: "Atypical" or "melancholic" features. Clin. Endocrinol. **43**: 433–442.
50. DORN, L. D., E. S. BURGESS, T. C. FRIEDMAN, B. DUBBERT, P. W. GOLD & G. P. CHROUSOS. 1997. The longitudinal course of psychopathology in Cushing's syndrome after correction of hypercortisolism. J. Clin. Endocrinol. Metab. **82**: 912–919.
51. MAGIAKOU, M. A., G. MASTORAKOS, D. RABIN, B. DUBBERT, P. W. GOLD & G. P. CHROUSOS. 1996. Hypothalamic corticotropin releasing hormone suppression during the postpartum period: Implications for the increase of psychiatric manifestations during this time. J. Clin. Endocrinol. Metab. **81**: 1912–1917.
52. CHIKANZA, I. C., P. PETROU, G. P. CHROUSOS, G. KINGSLEY & G. PANAYI. 1992. Detective hypothalamic response to immune/inflammatory stimuli in patients with rheumatoid arthritis. Arthritis and Rheum. **35**: 1282–1288.
53. CROFFORD, L. J., K. T. KALOGERAS, G. MASTORAKOS, M. A. MAGIAKOU, J. WELLS, K. S. KANIK, P. W. GOLD, G. P. CHROUSOS & R. L. WILDER. 1997. Circadian relationships between interleukin (IL)-6 and hypothalamic–pituitary–adrenal axis hormones: Failure of IL-6 to cause sustained hypercortisolism in patients with early untreated rheumatoid arthritis. J. Clin. Endocrinol. Metab. **82**: 1279–1283.